Guidelines for the Management of COVID-19 in Pediatric Patients

Version 2

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Health Policies and Standards Department

Health Regulation Sector (2022)

INTRODUCTION

Health Regulation Sector (HRS) forms an integral part of Dubai Health Authority (DHA) and is mandated by DHA Law No. (6) of 2018 to undertake several functions including but not limited to:

- Developing regulation, policy, standards, guidelines to improve quality and patient safety and promote the growth and development of the Health Sector.
- Licensure and inspection of health facilities as well as healthcare professionals and ensuring compliance to best practice.
- Managing patient complaints and assuring patient and physician rights are upheld.
- Governing the use of narcotics, controlled and semi-controlled medications.
- Strengthening health tourism and assuring ongoing growth.
- Assuring management of health informatics, e-health and promoting innovation.

ACKNOWLEDGMENT

The Subject Matter Experts panel of the COVID-19 Command and Control Center developed this document in collaboration with Health Policy and Standards Department (HPSD). HPSD would like to acknowledge and thank this panel of health professionals for their dedication toward improving quality and safety of healthcare services in the Emirate of Dubai.

Health Regulation Sector

Dubai Health Authority

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EXECUTIVE SUMMARY

In March 2020, the World Health Organization (WHO) declared COVID-19 as a global pandemic. Clinical evidence and research indicate that COVID-19 is known to be transmitted through direct contact with respiratory droplets of an infected person through coughing and sneezing and from touching surfaces contaminated with the virus. To ensure protective and preventative measures are adopted within the community, DHA has developed this document which recommends measures to be taken to protect the pediatric patients, staff and healthcare professionals from COVID-19, as health facilities re-engage in providing routine care.

There are recommendations within the guideline, each addressing an important component to build an effective and efficient system to prevent, prepare and respond to COVID-19. The guideline seeks to adopt best practices in the Emirate of Dubai.

Version 2 updates:

The panel has reviewed updated evidence and has amended the previous guidelines to include the new evidence. The following changes have been made:

- Consideration of starting Sotrovimab in mild illness. ID should be consulted.
- Sotroviman or Tocilizumab are not indicated in moderate illness.
- Use of Remdesivir and Tocilizumab needs ID consultations. There usage depends if the patient is ventilated or no.
- FDA approval for the use of Remdesivir is only for hospitalized patient and it is base on weight, age and risk factors for severe illness.

- The median duration of fever for the diagnosis of MIS-C is 4-6 days.
- There is limited rule of antiviral therapy in MIS-C.
- Usage of Ideal body weight is used for the MIS-C management.
- Patients being investigated as possible MIS-C should be admitted to the hospital if they presented with the signs mentioned in section 6.2.
- Stepwise approach should be used in the management of MIS-C with Immune modifying agents.

DEFINITIONS

COVID-19: is confirmed infection with SARS-CoV-2

Multi-system inflammatory syndrome in Children (MIS-C): is severe complications of COVID-19 infection specifically seen in Pediatrics. The exact definition is defined below:

MIS-C is the terminology used in the USA; in the UK, it is known as Pediatric Inflammatory Multisystem Syndrome (PIMS).

Pediatric ARDS:

Onset: within 1 week of a known clinical insult (that is, pneumonia) or new or worsening respiratory symptoms.

Chest imaging: (radiograph, CT scan or ultrasound): bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules.

Origin of pulmonary infiltrates: respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (for example, echocardiography) to exclude hydrostatic cause of infiltrate or oedema if no risk factor present.

Oxygenation Index (OI) preferred over Oxygen Saturation Index (OSI)

Bi-level (NIV or CPAP) more than or equal to 5 cmH_2O via full face mask: PaO_2/FiO_2 300 mmHg or less or SpO_2/FiO_2 264 or less.

OI= percentage of fraction of inhaled oxygen multiplied by the mean airway pressure (in mmHg), divided by the partial pressure of arterial oxygen (in mmHg)

OSI: OSI replaces PaO_2 with oxygen saturation as measured by pulse oximetry (SpO_2) in the OI equation

- Mild ARDS invasively ventilated: -4≦OI <8 **Or** -5≦OSI< 7.5
- Moderated ARDS invasively ventilated: -8≦OI <16 **Or** -7.5≦OSI< 12.3
- Severe ARDS invasively ventilated: -OI ≧ 16 **Or** OSI ≧12.3

Response to treatment: is the normalization of vital signs, CRP, and blood test and the resolution of symptoms and signs.

Septic shock: is any hypotension (SBP below fifth centile or more than 22 SD below normal for age) or 2 or 3 of the following:

- Altered mental status
- Bradycardia or tachycardia (heart rate less than 90 bpm or more than 160 bpm in babies and heart rate less than 70 bpm or more than 150 bpm in children)
- Prolonged capillary refill (more than 2 seconds) or weak pulse
- Fast breathing
- Mottled or cool skin or petechial or purpuric rash
- High lactate
- Reduced urine output
- Hyperthermia or hypothermia.

Sepsis: is the suspected or proven infection and two or more age-based systemic inflammatory response syndrome (SIRS) criteria, of which one must be abnormal temperature or white blood cell count.

SIRS criteria: is abnormal temperature (more than 38.5°C or less than 36°C); tachycardia for age or bradycardia for age if less than one (1) year; tachypnea for age or need for mechanical ventilation; abnormal white blood cell count for age or more than 10% bands.

ABBREVIATIONS

AKI	:	Acute Kidney Injury
ALP	:	Alkaline Phosphatase
ALT	:	Alanine Transaminase
ARDS	:	Acute Respiratory Distress Syndrome
ASA	:	Acetyl Salicylic Acid
AST	:	Aspartate Aminotransferase
BNP	:	B-Type Natriuretic Peptide
BP	:	Blood Pressure
CA	:	Coronary Artery
CAA	:	Coronary artery aneurysm
CBC	:	Complete blood count
CMP	:	Complete metabolic panel
CMV	:	Cytomegalovirus
COVID-19	:	Corona Virus Disease 2019
CPK	:	Creatinine phosphokinase
CPS	:	Canadian Paediatric society
CRP	:	C Reactive Protein
CT	:	Computerized tomography
CXR	:	Chest X ray
CYP 450	:	Cytochrome P450
DHA	:	Dubai Health Authority
DOAC	:	Direct-acting oral anticoagulant
EBV	:	Epstein Barr virus
ECG	:	Electrocardiogram
ECMO	:	Extracorporeal Membrane Oxygenation
ED	:	Emergency department

EF	:	Ejection Fraction
EKG	:	Electrocardiography
ESR	:	Erythrocyte sedimentation rate
ET aspirates	:	Endotracheal aspirates
EUA	:	Emergency use authorization
FBC	:	Full blood count
GA	:	Gestational Age
GI	:	Gastrointestinal
HFNC	:	High Flow Nasal Cannula
HPSD	:	Health Policies and Standards Department
HRS	:	Health Regulation Sector
ICU	:	Intensive care unit
ID	:	Identification
IgG	:	Immunoglobulin G
IgM	:	Immunoglobulin M
IL-6	:	Interleukin 6
INR	:	International normalized ratio
IPC	:	Infection Prevention and Control
IV	:	Intra Venous
IVIG	:	Intravenous Immunoglobulin
JVP	:	Jugular venous pressure
KD	:	Kidney disease
LDH	:	Lactate Dehydrogenase
LMWH	:	Low Molecular Weight Heparin
LV	:	Left Ventricular
MDI	:	Metered Dose Inhaler
MIS-C	:	Multi-System Inflammatory Syndrome in Children

MRI	:	Magnetic Resonance Imaging
Neb	:	Nebulizer
NG	:	Nasogastric
NP swab	:	Nasopharyngeal swab
NS	:	Normal Saline
O2	:	Oxygen
OI	:	Oxygenation Index
OSI	:	Oxygen Saturation Index
PCR	:	Polymerase Chain Reaction
PCT	:	Proactive Community Testing
PICU	:	Pediatric Intensive Care Unit
PIMS	:	Pediatric Inflammatory Multisystem Syndrome
PMA	:	Post Menstrual Age
PO	:	Per oral
PPI	:	Proton pump inhibitors
PRES	:	Posterior reversible encephalopathy syndrome
Pro BNP	:	Pro B type natriuretic peptide
PT	:	Prothrombin time
PTT	:	Partial Prothrombin time
QT	:	QT interval in the ECG
RR	:	Respiratory Rate
SARS-COV-2	:	Severe Acute Respiratory Syndrome Corona Virus 2
SBP	:	Systolic blood pressure
SD	:	Standard deviation
SIRS	:	Systemic Inflammatory Response Syndrome
SNP	:	Sodium nitroprusside
SpO2	:	Oxygen Saturation

SQ	:	Subcutaneous
TG	:	Triglyceride
UA	:	Urine analysis
UK	:	United Kingdom
USA	:	United States of America
VKA	:	Vitamin K antagonist
VTE	:	Venous Thromboembolism
UNL	:	Upper normal limit

1. BACKGROUND

Coronavirus disease 2019 (COVID-19) is an illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Fewer cases of COVID-19 have been reported in children (age 0-17 years) compared to adults. The true incidence of SARS-CoV-2 infection in children is not known due to lack of widespread testing and the prioritization of testing for adults and those with severe illness. Hospitalization rates in children are significantly lower than hospitalization rates in adults with COVID-19, suggesting that children may have less severe illness from COVID-19 compared to adults. A small number of pediatric patients may present with specific complications from COVID-19, such as Multi-system Inflammatory Syndrome (MIS-C). The severity of COVID-19 and MIS-C are variable in children.

2. SCOPE

2.1. To ensure the safe and efficient management of pediatric patients with COVID-19 in DHA licensed Health Facilities.

3. PURPOSE

3.1. Ensure safety of the pediatric patient.

3.2. Ensure that there is a standardized protocol for relevant healthcare professionals to deal with pediatric patients presenting with COVID-19 and its complications.

4. APPLICABILITY

4.1. DHA licensed Healthcare Professionals providing pediatric services.

4.2. DHA licensed Health Facilities providing pediatric services.

5. RECOMMENDATION ONE: MANAGEMENT OF COVID-19 IN PEDIATRIC PATIENTS (SEE APPENDIX FOR ALGORITHM)

5.1. Clinical manifestation of COVID-19 in Pediatrics:

5.1.1. Incubation period: 1-14 days (average 6 days)

5.1.2. Clinical manifestation varies from asymptomatic to symptomatic.

5.1.3. The list below highlights the commonly encountered symptoms: **BOLD** Fonts indicate the commonly reported symptoms.

Fever	Fatigue
Cough	Headache
Sore throat	Mylagia
Diarrhoea	Abdominal pain
Nausea/Vomiting	Poor appetite/feeding
Skin rash	Shortness of breath
Nasal congestion rhinorrhoea	New loss of smell/taste

Note: Specific features associated with MIS-C will be discussed separately.

5.2. Covid-19 disease severity:

5.2.1. Disease severity which varies with virus variant:

Severity	Mild	Moderate	Severe-Critical
% of cases	**51%**	**39%**	**6%**
Description	• No respiratory distress	• Needs IV fluid support.	• Needs respiratory support not

	• No oxygen requirement • Able to self-hydrate.	• Needs respiratory support	improving with nasal cannula. • Needs invasive ventilation • Clinical worsening

5.2.2. Risk factors for severe illness:

Medical complexity with genetic/metabolic, neurologic, and congenital heart diseases or medically significant heart disease	
Obesity	Diabetes
Respiratory disorder like asthma	Hematologic disorder
Hepatic disorder	Immunosuppression
Renal disorder or on dialysis	Children younger than 2 years old

5.3. Manifestations that are more common in infants and toddlers:

5.3.1. Respiratory failure

5.3.2. Myocarditis

5.3.3. Shock

5.3.4. Acute renal failure

5.3.5. Coagulopathy

5.3.6. Multi-organ system failure.

5.3.7. MIS-C

5.4. Specific dosage, indications and monitoring of medications used is illustrated in a separate table.

Clinical presentation	**Investigations and therapeutic agents**	**Comments**

Asymptomatic		
• Tested for reasons other than symptoms	• No additional test or treatment. • Supportive care	Patient with high risk factors needs close observation and follow up.
Mild illness		
• Nonspecific symptoms as mentioned above • No signs of dehydration or breathing difficulties • Does NOT need hospitalization	• Supportive care with adequate fluid and calorie intake. • Use MDI if needed instead of Nebulizers. • Steroid not indicated unless used for other illness like croup or asthma. • Add antibiotics if Pneumonia is suspected. • Fever managed with Paracetamol as first line then Ibuprofen s second line.	• Home monitoring. • Close monitoring for high risk patients • Evaluate for MIS-C if needed **Avoid Ibuprofen in patients with AKI or poor fluid intake.**
Mild Pneumonia		
Hospitalized patient	• Supportive care Consult ID for Steroid +/- Remdesivir if on Respiratory support	
Moderate illness/Non severe pneumonia		
• Cough/dyspnoea and tachypnoea (based on age table below) • Needs IV fluid support • Needs respiratory support	**Admit** **Base line investigations:** FBC, CRP, IgG level PT/PTT/INR/Fibrinogen/D-Dimer CXR • Supportive care with adequate fluid and calorie. • Ensure Euvolemia. • **Respiratory** support if needed.	

- **Antibiotics** for suspected pneumonia (Table below)
- **Oseltamivir** when influenza is circulating until NP swab influenza PCR test is negative.
- Consider adding **azithromycin** if age >5yrs
- Add **dexamethasone** if on respiratory support.
- **Consider IVIG replacement** if initial IgG is below the range.(Table below)
  - Dose: IVIG 400mg/kg * 1 dose
- **Remdesivir**
  - Consult ID
  - Assess eligibility for Remdesivir for 5 days
- **Anticoagulant:**
  - Assess the risk for TEV and start accordingly

NO Sotrovimab or Tocilizumab

Age	RR/minutes
<2 months	>=60
2-11 month	>=50
1-5 year	>=40
6-12 year	>=35
13-18 year	>= 30

Age	IgG mg/dl
0-1 month	<400
1-7 month	<200
7 month to less than 3 year	<250
3-6 years	<350
>= 6 years	<500

- Evaluate **for MIS-C if needed**
- Needs close observation as it can worsen rapidly
- Signs of **clinical worsening**
- Persistent high fever
- Worsening respiratory distress
- Increasing O_2 needs

Repeat **Labs** as clinically indicated.

Suggested choices of antibiotics

Ampicillin and Ceftazidime/Cefdinir for ongoing oral treatment
Age <= 28 days or preterm infant (GA <37 week) with PMA <41 weeks
Ceftriaxone/Cefdinir for ongoing oral treatment
Age >28 days or preterm GA <35 weeks with PMA >=41 week- 4 months Age 4 month and not received 2 Hib and Pneumococcal vaccine

Amoxicillin/Cefuroxime/Cefprozil		
Age 4 month and fully immunized for age		
Severe illness/Severe pneumonia/Critical illness		
Critical illness like Sepsis/ARDS/Shock Detailed definition as under section Definition.	**Severe illness** is having >=1 of the following: 1. SpO2 ≤ 94% on room air 2. Requiring supplemental oxygen 3. Requiring mechanical ventilation 4. Requiring ECMO 5. General danger signs: inability to feed/drink, lethargy, convulsions or altered consciousness.	
Investigations: Full evaluation for MIS-C Daily lab as clinically indicated. - FBC, CRP, PCT, urea and electrolytes, creatinine, PT/PTT/fibrinogen/D-dimer, - IgG, LDH, IL-6, ferritin, TG, CPK, troponin, Pro-BNP, lactate - Urine analysis - Blood culture and Viral study: respiratory viral screen, CMV, EBV - ECG and Cardiac Echo • CXR: While the diagnosis is made on clinical grounds, chest imaging (radiograph, CT scan or ultrasound) may assist in diagnosis and identify or exclude pulmonary complications.		
Therapeutic Agents		
Treat Sepsis/Shock as per the international guidelines		
Systemic Corticosteroid	**Preferred:** Dexamethasone **Alternative:** Prednisolone/ Methylprednisolone/ Hydrocortisone	**Duration:** 10 days **Indications**: Patient on Oxygen or Mechanical ventilation.
Gastric ulcer prophylaxis	Proton Pump inhibitors	-While on Steroids
Empiric antibiotics	As mentioned above	
Oseltamivir	* ***Non-intubated*** patient: give until NP swab is influenza PCR is negative	-Recommended if influenza is co-circulating

	* ***Intubated*** patient: give until NP swab *and* ET aspirates is influenza PCR negative.	
IV Immunoglobulin	As stated in moderate illness/non-severe pneumonia.	
Remdesivir (not supported by evidence)	• Consult ID • Assess eligibility for remdesivir.	Consider it but **NOT** if on invasive mechanical ventilation
Tocilizumab (not supported by evidence)	• Consult ID • 2nd choice after remdesivir	• Consider it if on HFNC or non-invasive ventilation if the patient in critical condition.
Anticoagulant	Assess the risk for TEV and start accordingly. *Review MIS-C guideline below*	

5.5. Therapeutic agents used in COVID-19 in Pediatrics.

Therapeutic Agent	Dose	Comments
Corticosteroids		
Preferred		
Dexamethasone	• 0.15 mg/kg/dose once daily • Max dose 6 mg • IV/NG/PO **Duration:** For up to 10 days	**Indications:** 1. Respiratory support: Oxygen or invasive mechanical ventilations or ECMO. **Notes:** - In preterm, risks vs benefits should be considered based on GA, postnatal age and illness severity. -Preterm infant corrected GA <40 weeks, use hydrocortisone -Start on Gastric ulcer prophylaxis while on corticosteroids.
Alternatives		
Prednisolone	• 1 mg/kg once daily • Max 40 mg/dose • NG/PO **Duration:** For up to 10 days	

Methylprednisolone	• Second choice after Dexamethasone • 2 mg/kg/day Q 12 hr • Max 60 mg/day • IV **Duration:** For up to 10 days	**Adverse effects:** 1. Hyperglycaemia: Many patients need insulin infusion 2. Hypertension: Best managed with calcium channel blocker
Hydrocortisone	• 0.5 mg kg/dose • IV **Duration:** • If q12 hr, for 7 days • If once daily for 3 days	
IV Immunoglobulin		
IV Immunoglobulin **IVIG**	• 400 mg/kg/dose • One dose • Based on ideal body weight	**Indications:** 1. Can be used in the non-severe pneumonia, moderate-severe illness. 2. If initial IgG is below age-based thresholds. **Adverse effects:** 1. Infusion reactions 2. Anaphylaxis 3. Transaminitis 4. Aseptic meningitis 5. Haemolysis

Remdesivir **Anakinra** Not supported by evidence Useful websites: COVID-19 drug interaction http://www/covid19-druginteractions.org	• **Consult ID** **FDA approval applies to Hospitalized paediatric patients:** • Age ≧12 years AND weight ≧40kg with risk factors for severe illness or high need of Oxygen. • Age ≧ 16 years if high need of Oxygen even if no risk factors for severe disease.	**Indications:** 1-Can be used for patients on respiratory support after ID consultation. **Monitoring:** • Labs before initiation and daily • FBC, AST, ALT, alkaline phosphatase, bilirubin (total and direct), PT • Consider discontinuation if ALT > 10 times upper limit of normal during treatment. • Discontinue if ALT elevation is accompanied with signs of liver inflammation.

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<table>
<tr><th>Weight KG</th><th>No ECMO/MV</th><th>ECMO/MV</th></tr>
<tr><td rowspan="3">3.5->40 hg</td><td colspan="2">Needs EUA</td></tr>
<tr><td colspan="2">Loading dose 5mg/kg IV once</td></tr>
<tr><td>2.5mg/kg/dose IV Q24 hr for 4 days-
Extend to 10 days if no improvement after 5 days treatment.</td><td>2.5mg/kg/dose IV Q24 hr for 9 days</td></tr>
<tr><td rowspan="2">>=40 kg</td><td colspan="2">Loading dose 200 mg IV once</td></tr>
<tr><td>100 mg IV q24 hr for 4 days.
Extend to 10 days if no improvement after 5 days treatment</td><td>100mg/kg/dose IV Q24 hr for 9 days</td></tr>
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- **Avoid** use with acetaminophen up to 15 days post-remdesivir treatment

Adverse effects:

- Increased liver enzymes stop it if ALT 10 times the normal upper limits.
- Infusion related hypotension
- Drug-drug interactions CYP450
- QT prolongation
- Risk of Torsade's de points

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Tocilizumab

IL-6 inhibitor

Not supported by evidence

Useful websites:

COVID-19 drug interaction

http://www/covid19-druginteractions.org

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-Consult ID

-Duration: once

Consider additional dose about 8-12 hours after if continued clinical decompensation.

-Dosage based on age and weight.

Dosage for age <18 year, as below

<table>
<tr><th>Weight</th><th>Dose</th></tr>
<tr><td><30 kg</td><td>12 mg/kg</td></tr>
<tr><td>>=30 kg</td><td>8 mg/kg</td></tr>
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Criteria for high risk of cytokine storm:

>=1 of the following:

IL-6	≧3 XUNL
Ferritin	>300 ug/L with doubling in 24hr
Ferritin + LDH	>600 ug/L at presentation >250
D-Dimer	Elevated

UNL upper normal limits

Caution:

1. Avoid live viral vaccines

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		2. Caution when converting from tocilizumab to anakinra 3. IL-6 and CRP are **NOT** reliable AFTER tocilizumab. **Adverse effects:** 1. Infusion reaction. 2. GI perforation 3. Anemia 4. Hepatitis

5.6. Therapies not supported by evidence in paediatric patients (CPS 2021)

5.6.1. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers.

5.6.2. Interleukin IL-1 receptor antagonists such as anakinra.

5.6.3. IL-6 receptor antagonists such as tocilizumab and sarilumab.

5.6.4. Other monoclonal antibodies including casirivimab and imdevimanb.

5.6.5. Nebulized interferon beta one alpha.

5.6.6. Colchicine.

5.6.7. Lopinavir and ritonavir.

5.6.8. Ivermectin.

5.6.9. Hydroxychloroquine.

5.6.10. Antibiotics are not recommended to treat cases of COVID-19 without clinical suspicion of bacterial co-infection.

6. RECOMMENDATION TWO: MANAGEMENT OF MULTISYSTEM INFLAMMATORY SYNDROME (MIS-C) IN CHILDREN < 21 YEARS

6.1. MIS-C: Clinical–Diagnostic/disposition recommendations for Suspected Multisystem Inflammatory Syndrome in Children <21 years.

6.1.1. Case Definition:

a. An individual aged <21 years presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological); AND

b. No alternative plausible diagnoses; AND

c. Positive for current or recent SARS-CoV-2 (COVID-19) infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms.

6.1.2. Clinical features-May include the following:

a. Persistent fever > 39 C >24hrs (Median duration from 4-6days).

b. Kawasaki disease-like features: conjunctivitis, red eyes; red or swollen hands and feet; rash (except vesicular rash); red cracked lips, swollen glands. Coronary artery enlargement and/or aneurysms.

c. Gastrointestinal symptoms such as abdominal pain, diarrhea, nausea/vomiting (patients have presented with colitis, hepatitis, and questionable appendicitis).

d. Toxic shock syndrome-like features with hemodynamic instability and poor heart function. Cytokine storm/macrophage activation or hyper-inflammatory features.

e. Thrombosis or acute kidney injury.

f. Shortness of breath suggestive of congestive heart failure or pulmonary embolism.

g. Respiratory symptoms typically reported in adults with COVID-19 may not be present in pediatric patients with MIS-C.

h. Neurocognitive symptoms: lethargy, headache and confusion.

6.1.3. Consider MIS-C as part of your differential diagnosis if:

a. MIS-C is a rare complication temporally associated with COVID-19. Any child with suspected MIS-C should also be evaluated for infectious and non-infectious etiologies.

b. Bacterial sepsis, bacterial enteritis, toxic shock syndrome, Kawasaki, Kawasaki like, hemo-phagocytic lympho-histotocytosis, macrophage activation syndrome.

c. Vasculitis, Lupus.

d. Viral syndrome (e.g. CMV, EBV, Adenovirus, Coxackivirus, etc.)

e. Acute Appendicitis.

6.1.4. Emergency warning signs of MIS-C

a. Severe abdominal pain

b. Difficulty breathing

c. Cyanosis & O2 saturation <92%

d. New confusion

e. Inability to wake up or stay awake

f. Hypotension, other unstable vital signs.

6.1.5. Outpatient services evaluation for MIS-C:

a. Evaluate a child with persistent fever (≥3 days) who is moderately to severely ill with clinical signs of organ dysfunction (e.g. gastrointestinal, respiratory, cardiac, skin, or neurologic).

b. Initial evaluation should include measurement of vital signs, assessment of perfusion and oxygen saturation. Early consultation and coordination with the nearest pediatric referral center for optimal testing and management should be considered.

6.2. Patients under investigation for MIS-C should be considered for admission to the hospital for further observation while completing the diagnostic evaluation, especially if they display the following (H):

6.2.1. Abnormal vital signs (tachycardia, tachypnea).

6.2.2. Respiratory distress of any severity.

6.2.3. Neurologic deficits or change in mental status (including subtle manifestations) or evidence of renal or hepatic injury (including mild injury).

6.2.4. Markedly elevated inflammatory markers or abnormal EKG, B-type natriuretic peptide (BNP), or troponin T.

6.3. Investigations:

Tier 1	Tier 2
• CRP, ESR • CBC • Virology for SARS-CoV-2 PCR (nasopharyngeal), and /or blood serology for SARS-CoV-2: (Serologic tests must be sent prior to administration of intravenous immunoglobulin IVIG). • Complete Metabolic Panel (CMP) **CRP >=3mg/dl or ESR >=40mm/ hr, neutrophilia, ALC <1,000/ul, Platelet <150,000, sodium <135mmol, hypoalbuminemia**	• Complete lab evaluation • BNP, troponin, Procalcitonin • PT, PTT, d-dimer, ferritin • Fibrinogen, uric acid, LDH, cytokine panel, triglycerides, SARS-CoV-2 serology, blood smear, ECG, echocardiogram

6.4. **Management and level of care:**

6.4.1. **Exclude** potential septic foci and careful cardiac assessment (liver, JVP, cardiac/thoracic ratio on CXR).

6.4.2. Resuscitation: Supportive, oxygen if needed, paracetamol.

a. If signs of shock – fluid resuscitation (10ml/kg NS) with re- evaluation after each bolus.

b. IV Fluid: Maintain euvolemia

c. If no improvement with fluid, start inotropes: dopamine at 5-10mcg/kg/min, until central access (consider Epinephrine).

6.4.3. **Empiric Antibiotics**: patients presenting with severe multisystem involvement and shock should receive empiric broad- spectrum antibiotic therapy pending.

6.4.4. **Limited role of antiviral therapy**: Because MIS-C likely represents a post infectious complication rather than infection, the role of antiviral therapies (e.g. remdesivir) is limited.

6.4.5. **Immune-modifying therapy in MIS-C**

a. Patients under investigation for MIS-C without life-threatening manifestations should undergo diagnostic evaluation for MIS-C as well as other possible infectious and non-infectious etiologies before immunomodulatory treatment is initiated.

b. Patients under investigation for MIS-C with life-threatening manifestations may require immunomodulatory treatment for MIS-C before the full diagnostic evaluation can be completed.

c. Some patients with mild symptoms may require only close monitoring without immunomodulatory treatment. Uncertainty noted around the empiric use of intravenous immunoglobulin (IVIG) in this setting to prevent CAAs.

d. A stepwise progression of immunomodulatory therapies should be used to treat MIS-C with IVIG and low moderate dose glucocorticoids considered first tier therapy in most hospitalized patients.

6.4.6. **Intravenous Immunoglobulin:**

a. Early IVIG 2g/kg (ideal body weight). once over 12-18 hours), max 100 gram. Monitor for fluid overload, consider Lasix.

b. Patient cardiac function and fluid status influence the duration of the infusion of IVIG therapy.

c. Or the dose can be divided over 2 days.

d. Can use diuretics to avoid volume overload.

e. In selected patients with mild disease or contraindication with glucocorticoid, IVIG alone may be appropriate as first line treatment for MIS-C.

f. These patients should be monitored closely, and intensification therapy should be added at first sign for clinical worsening.

g. In patients with refractory MIS-C despite a single dose of IVIG, a second dose of IVIG is not recommended.

6.4.7. **Glucocorticoid:**

a. Low-moderate dose glucocorticoids (1-2 mg/kg/day) should be given with IVIG as dual therapy for treatment of MIS-C in hospitalized patients.

b. In patients who do not respond to IVIG and low-moderate dose glucocorticoids, high dose, IV pulse glucocorticoids (10-30 mg/kg/day) should be considered, especially if a patient requires high dose or multiple inotropes and/or vasopressors.

c. Serial laboratory testing and cardiac assessment should guide immunomodulatory treatment response and tapering.

d. Tapering of glucocorticoids consider methylprednisolone over 2-3 weeks (around 10-25% every 3 days).

e. Oral steroid therapy: Transition from IV methylprednisolone to oral prednisolone (liquid) or oral prednisone (tablet) using the following conversion: 4 mg methylprednisolone = 5 mg prednisolone or prednisone.

f. The purpose of the prolonged steroid taper in MIS-C is prevention of rebound inflammation.

g. For refractory or rapidly progressive cases who pulse steroid given, taper dose to 2 mg/kg/day and then taper over 4-8 weeks on a case-by-case basis with rheumatology involvement and endocrinology.

6.4.8. **Adjunctive Therapy:**

a. High dose anakinra (>4 mg/kg/day IV or SQ) should be considered for treatment of MIS-C refractory to IVIG and glucocorticoids, or in patients with contraindications to long-term use of glucocorticoids.

b. Infliximab (5-10 mg/kg/day IV x1 dose) may be considered as an alternative biologic agent to anakinra for treatment of MIS-C refractory to IVIG and glucocorticoids or in patients with contraindications to long-term use of glucocorticoids. Infliximab should not be used to treat patients with MIS-C and features of MAS.

6.4.9. **Antiplatelet and anticoagulation therapy:**

a. Low dose aspirin (3-5 mg/kg/day; max 81 mg/day) should be used and continued until normalization of platelet count and confirmed normal coronary arteries at ≥4 weeks after diagnosis.

b. Treatment with aspirin should be avoided in patients with active bleeding, significant bleeding risk, and/or platelet count ≤80,000/μL.

c. Patients with central venous catheterization, age >12 years, malignancy, ICU admission, and D-dimer level elevated to greater than 5 times the upper limit of normal are high risk factors for thrombosis in MIS-C, then consider higher intensity anticoagulation in an individual basis.

d. Patients with CAAs should receive anticoagulation therapy.

e. Patients with a maximal z score of 2.5-10.0 should be treated with low dose aspirin.

f. Patients with a z-score ≥10.0 should be treated with low dose aspirin and therapeutic anticoagulation with enoxaparin (factor Xa level 0.5-1.0) for at least 2 weeks, and then can be transitioned to vitamin K antagonist

(VKA) therapy (INR 2-3) or direct-acting oral anticoagulant (DOAC) as long as CAA z-score exceeds 10.

g. MIS-C patients with an ejection fraction <35% should receive low dose ASA and therapeutic anticoagulation* until EF exceeds 35%.

h. MIS-C patients with thrombosis should receive low-dose ASA and therapeutic anticoagulation* for 3 months, pending resolution of thrombosis. Repeat imaging of thrombosis at 4-6 weeks post diagnosis should be acquired, and anticoagulation can be discontinued if resolved.

i. For MIS-C patients who do not meet the above criteria, the approach to antiplatelet and anticoagulation management should be tailored to the patient's risk for thrombosis.

6.4.10. **Other Therapy:**

a. GI prophylaxis and calcium/Vitamin D until off steroid, Proton pump inhibitor (Esomeprazole I mg/kg/day, max 40 mg/day).

6.5. **Therapy Complications**

6.5.1. Fluid overload risk with IVIG infusion-consider diuretics

6.5.2. Hypertension: high dose methylprednisolone associated with severe hypertension and Posterior Reversible encephalopathy Syndrome (PRES). Treatment with Ca channel blockade (Amlodipine) or SNP if severe cardiac dysfunction.

6.5.3. Hyperglycaemia- may require insulin infusion.

6.5.4. Gastritis: patients should all receive high dose PPI.

6.5.5. Salicylate complications-AKI, Respiratory alkalosis.

6.6. **PICU management:**

Patient to be managed as COVID positive (even if PCR is negative for SARS- CoV-2). Ensure full PPE and management in an appropriate area.

6.6.1. Central access: awake femoral line preferable in self-ventilating.

6.6.2. Patients-most require Epinephrine.

6.6.3. Temperature control- regular paracetamol, active cooling if ventilated.

6.6.4. Ensure IVIG was administered otherwise give a dose above, monitor for fluid overload during infusion.

6.6.5. Methylprednisolone as per clinical severity.

6.6.6. Antiplatelet and anticoagulation as above.

6.6.7. Proton pump inhibitors as above.

6.7. Trending **of Labs and ECGs in ICU patients**

6.7.1. Urgent Echo upon admission to PICU. Repeat as clinically indicated.

6.7.2. 12 lead ECG at admission, repeat daily or if clinical concerns.

6.7.3. If oxygen requirement repeat CXR.

6.7.4. Regular blood gas- measure lactate.

6.7.5. Repeat core investigations 12 hourly- if rising inflammatory markers discuss with seniors and specialty services.

6.7.6. CBC w/diff, CRP, BMP, d-dimer, ferritin Q day until afebrile and labs improving x3 days.

6.7.7. Troponin Q6 hr, decrease as indicated.

6.7.8. BNP Q48 hr or sooner if clinical worsening.

6.7.9. Repeat other labs as indicated.

6.7.10. EKG Q48 hrs to monitor QT interval, or sooner if clinical worsening.

6.8. **Cardiac Manifestations and Management**

6.8.1. Pancarditis may include bi-ventricular impairment, mitral/tricuspid valve regurgitation, diastolic dysfunction, pericardial effusion, coronary artery dilatation/aneurysm,

6.8.2. Arrhythmias observed

a. Clinical course unpredictable with rapid deterioration observed in some.

b. Low threshold for Milrinone infusion.

c. Severe cases consider levosimendan after consultation with cardiology.

d. VA ECMO for refractory shock- cardiology.

e. Patients with MIS-C and abnormal BNP and/or troponin T at diagnosis should have these laboratory parameters trended over time until they normalize.

f. ECGs should be performed at a minimum of every 48 hours in patients who are hospitalized and during follow-up visits. If conduction abnormalities are present, patients should be placed on continuous

telemetry while in the hospital, and Holter monitors should be considered during follow-up.

g. Echocardiograms conducted at diagnosis and during clinical follow-up.

h. Echocardiograms should be repeated at a minimum of 7-14 days and 4-6 weeks after presentation. For those patients with cardiac abnormalities occurring in the acute phase of their illness, an echocardiogram 1 year after diagnosis could be considered. Patients with left ventricular (LV) dysfunction and/or CAA will require more frequent echocardiograms.

i. Cardiac MRI may be indicated 2-6 months after diagnosis in patients who presented with significant transient LV dysfunction in the acute phase of illness (LV ejection fraction <50%) or persistent LV dysfunction.

j. Cardiac CT should be performed in patients with suspicion of distal CAAs that are not well seen on echocardiogram.

6.9. **Transfer to Med Pediatric unit once criteria is met.**

6.9.1. No ongoing cardiac dysfunction or shock.

6.9.2. Normalized troponin.

6.9.3. Respiratory support at levels allowed on pediatric medical unit.

6.10. **Discharge criteria:**

6.10.1. CRP, ferritin, and d-dimer improving

6.10.2. Afebrile x 48 hours

6.10.3. Blood cultures without growth x 48 hours

6.10.4. ECG without arrhythmia

6.10.5. Latest echo stable/improved

6.10.6. Tolerating enteral diet

6.10.7. Not requiring oxygen

6.10.8. Follow-up coordinated.

6.11. **Initial Follow-up Plan**

6.11.1. Follow-up with pediatrician in 2-3 days with exam, full vital signs (including BP) and repeat CBC w/ diff, CRP, BMP. Repeat labs 1-2 times per week until normalized.

6.11.2. Follow-up with cardiology 1-2 weeks after discharge with repeat ECG and Echo.

6.11.3. Follow-up with Endocrinology 2 weeks after steroids started (if anticipated duration ≥ 3 weeks).

6.11.4. Follow-up 4-6 weeks with cardiology with Echo, consider cardiac MRI 1-3 months.

6.11.5. Discharge medications: low-dose aspirin until Cardiology discontinues, gastritis prophylaxis and Calcium/Vitamin D supplement until off steroids.

6.11.6. Patients will not routinely be discharged on anticoagulation (aside from aspirin).

6.11.7. If steroids are, used pediatrician will advise on the duration of the acute wean (generally 2-3 weeks if milder, 4-8 weeks on a case-by-case basis.

6.12. **Readmission considered:**

6.12.1. Any recurrent fever or other recurrence of symptoms (rash, Mucositis, conjunctivitis, vomiting/diarrhea, neurological changes, chest pain, etc.) should prompt urgent evaluation by primary provider. If patient is stable and can be assessed by outpatient provider within 6-12 hours that may be considered. Otherwise refer patient to local ED (if > 60 minutes away) or to Pediatric Hospital ED.

6.12.2. If seen in primary clinic with recurrence of symptoms, obtain full exam + VS including BP. If unstable transfer to ED. If stable and no alternate source of illness is suspected, may obtain labs: CBC w/diff, CRP, ESR, ferritin, procalcitonin, CMP. Consider troponin, d-dimer, UA, Urine Culture, Blood Culture, Rapid Strep.

6.12.3. Outpatient providers should contact consultant in hospital to discuss whether re-evaluation at hospital is needed. Worsening laboratory markers (e.g. increasing CRP) in absence of clinical signs should prompt outpatient discussion with specialists (ID, immunology, cardiology, hematology depending on the laboratory study).

6.13. **Family Education:**

6.13.1. No live-virus vaccines x 11 months if IVIG was given (pts at high risk of exposure may receive sooner and be reimmunized after 11 months if they have an inadequate serological response).

6.13.2. Risks of IVIG including haemolytic anaemia, aseptic meningitis.

6.13.3. Discuss plan for recurrent fever or other KD symptoms (rash, Mucositis) with family recommend pediatrician or ED ASAP evaluate any symptoms within 7 days of discharge.

6.13.4. Families should receive teaching on stress dose steroids.

6.13.5. Limit exercise and strenuous activity until cleared by cardiology (may be several weeks-months.

6.14. **Diagnostic Pathway for MIS-C:**

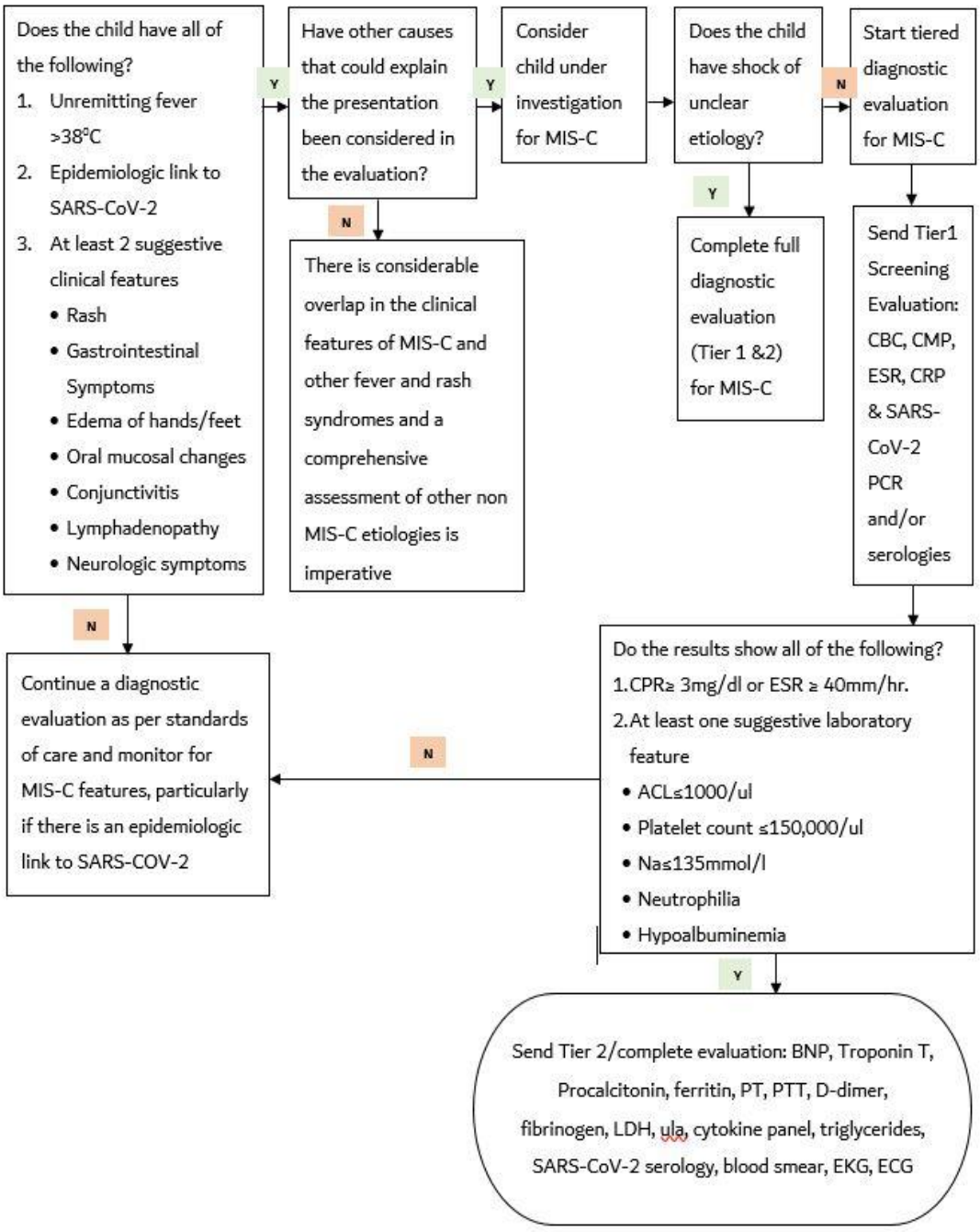
6.14.1. Due to the difficulty in establishing an epidemiological linkage to a preceding SARS-CoV-2 infection given the evolving COVID-19 pandemic, the diagnosis of MIS-C must be determined based on the totality of the history, exam, and laboratory studies. Patients may have MIS-C even in the absence of preceding COVID-19-like illness or a clear exposure history to SARS-CoV-2, especially in the setting of high community prevalence.

6.14.2. 2-Rash, (polymorphic, maculopapular, or petechial, but not vesicular); GI symptoms, (diarrhea, abdominal pain, or vomiting); oral mucosal changes, (red and/or cracked lips, strawberry tongue, or erythema of the oropharyngeal mucosa); conjunctivitis, (bilateral conjunctival injection without exudate); neurologic symptoms, (altered metal status, encephalopathy, focal neurologic deficits, meningismus, or papilledema).

6.14.3. Complete metabolic panel: Na, K, CO2, Cl, BUN, Cr, glucose, Ca, albumin, total protein, AST, ALT, ALP, Bilirubin.

6.14.4. Send procalcitonin and cytokine panel, if available.

6.14.5. If not sent in tier 1 evaluation. If possible, send SARS-CoV-2 IgG, IgM.



6.15. **Algorithm for Initial Immunomodulatory Treatment in MIS-C:**

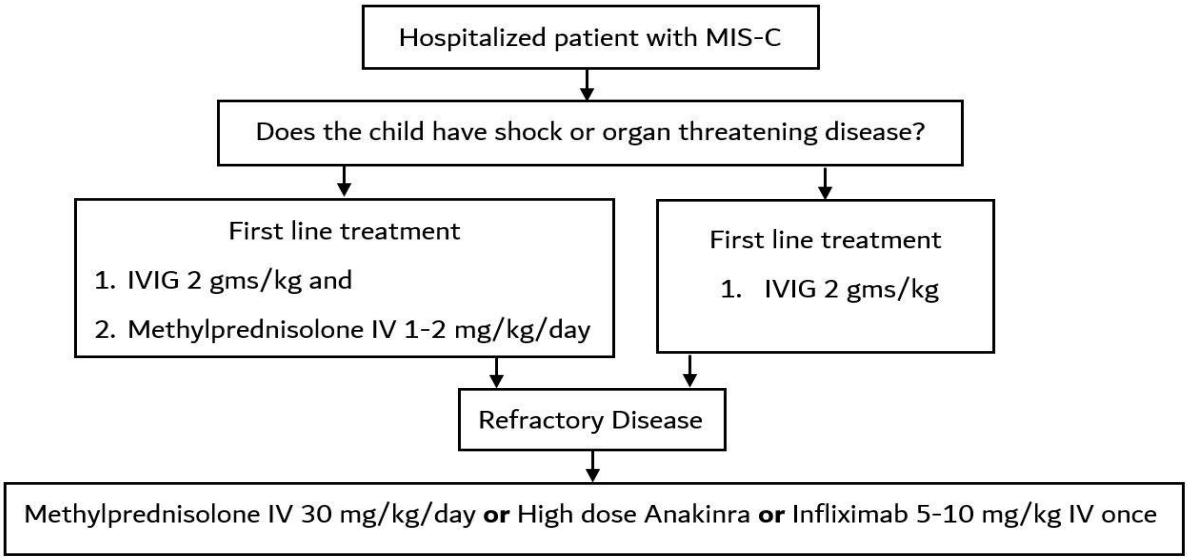
6.15.1. IVIG dosing is 2 gm/kg based on ideal body weight with maximum dose of 100gm. Cardiac function and fluid status should be assessed before IVIG is given. In some patients with cardiac dysfunction, IVIG may be given as in divided doses (1 gm/kg daily over 2 days).

6.15.2. Methylprednisolone or another steroid at equivalent dosing may be used.

6.15.3. In select patients with mild disease or contraindications to glucocorticoids, IVIG alone may be appropriate as first-line treatment for MIS-C. These patients should be monitored closely, and intensification therapy should be added at the first signs for clinical worsening.

6.15.4. Refractory disease is defined as persistent fevers and/or ongoing and significant end organ involvement.

6.15.5. Infliximab should not be used in patients with MIS-C and features of MAS.



6.16. **Suggested approach to antithrombotic therapy in hospitalized patients with MIS-C**

6.16.1. All patients who meet diagnostic criteria for MIS-C are treated with low-dose aspirin (3 to 5 mg/kg) unless they have a contraindication. This is extrapolated from the practice of using aspirin in the management of children with Kawasaki disease.

6.16.2. Indications for therapeutic anticoagulation in this setting are not standardized, and practice varies considerably. In addition to the circumstances listed above, some experts would also administer therapeutic anticoagulation to patients with severe manifestations of MIS-C if the D-dimer is markedly elevated (i.e., >10 times the upper limit of normal). Refer to Up-to-date topics and drug information monographs for suggested therapeutic and prophylactic dosing of LMWH.

6.16.3. In patients without an indication for therapeutic anticoagulation, and who are not critically ill, the decision to provide pharmacologic VTE prophylaxis is individualized, weighing the risk of thrombosis and risk of bleeding.

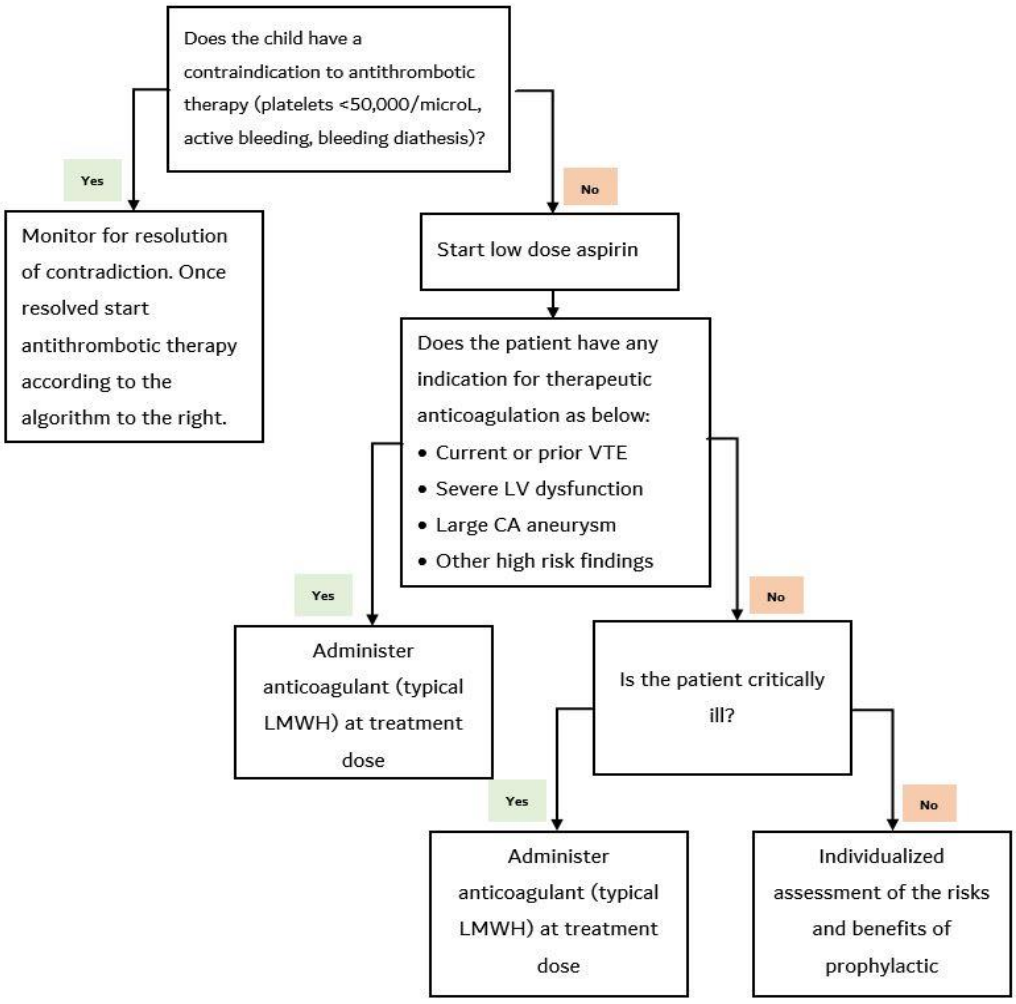
6.16.4. The diagnosis of COVID-19-related MIS-C itself should be considered a major risk factor for VTE.

6.16.5. Other important risk factors include the presence of a central venous catheter, underlying malignancy, prolonged immobility, obesity, and oral contraceptives.

6.16.6. VTE prophylaxis is appropriate for most adolescents hospitalized with MIS-C, if bleeding risk is not high.

6.16.7. In younger children, the decision is made on a case-by-case basis.

6.16.8. When VTE prophylaxis is used, LMWH is generally the preferred agent.



6.16.9. Non-pharmacologic strategies for VTE prophylaxis (e.g., intermittent pneumatic compression devices [size permitting] and early mobilization) are encouraged, but MIS-C-related hypercoagulability may merit a higher level of intervention.

6.16.10. For details regarding other risk factors for VTE, refer to additional Up-to-date content.

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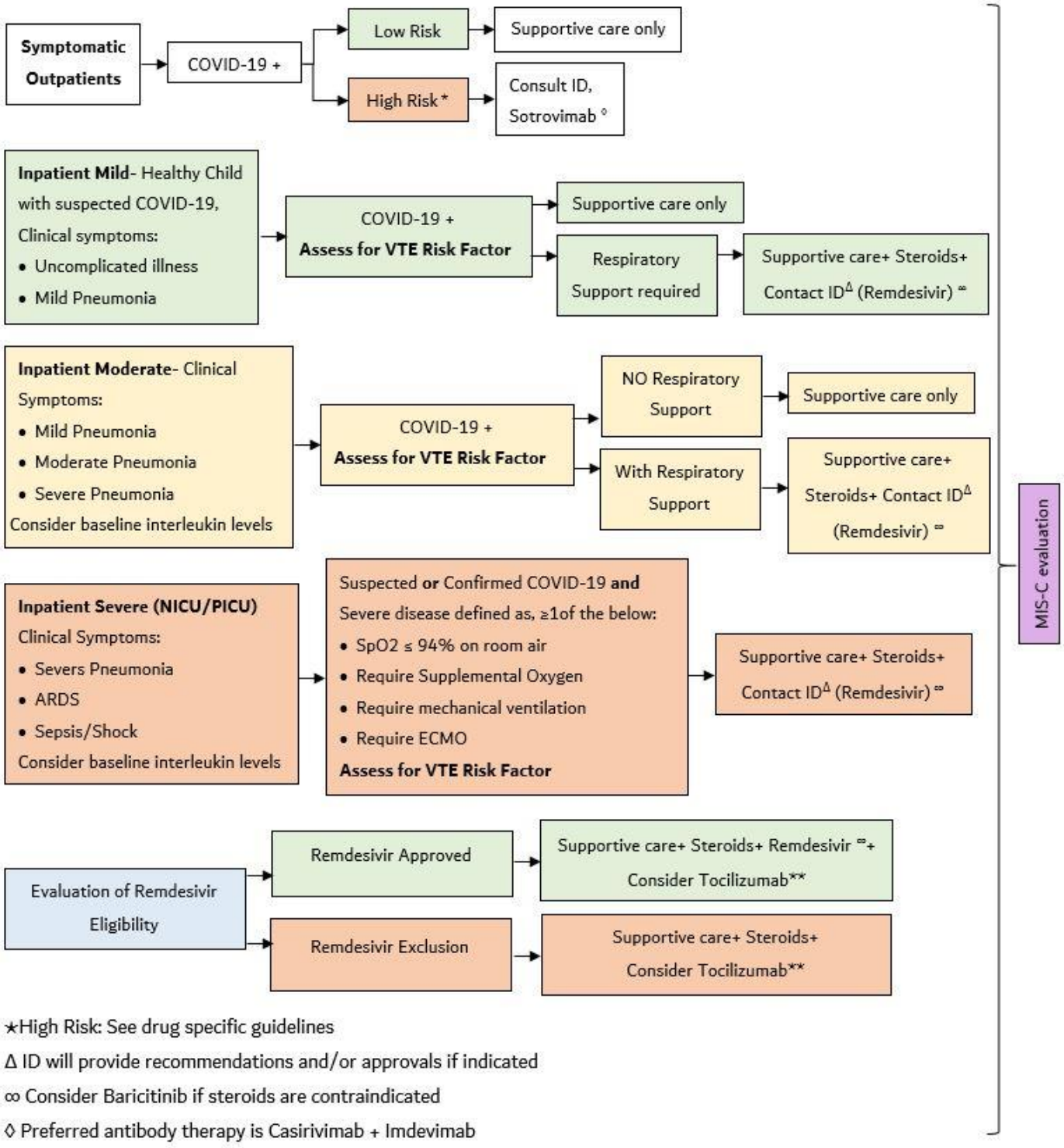
APPENDIX: SUMMARY OF TREATMENT ALGORITHM OF COVID-19



★High Risk: See drug specific guidelines

Δ ID will provide recommendations and/or approvals if indicated

∞ Consider Baricitinib if steroids are contraindicated

◊ Preferred antibody therapy is Casirivimab + Imdevimab

Adopted from CHKD treatment guideline for COVID-19 in Children Version 3.5.6/2/2020